# DEVICE FOR INTRODUCING A LIQUID INTO A PHARMACEUTICAL CONTAINER

This invention relates to an apparatus for use in filling pharmaceutical vials which have an elastomeric closure which can be punctured by a needle point and fluid medicament content thereby introduced into the vial.

Such a process is known from US-A-2002/0023409 in which the residual puncture site left by the needle is heat sealed using a laser beam.

Needles for this purpose are known, but a problem with such needles is that of achieving an optimised flow pattern of the fluid as it exits the needle when within the vial. A further problem is that the point and side orifices of known needles can cut through the vial closure during puncture in a way which forms particles of the closure material which can contaminate the medicament introduced into the vial or block or obstruct flow through the needle.

There are numerous disclosures of hollow, pointed ended needles having side orifices for the exit of fluid. For example US-A-5478328 and US-A-6,221,056 disclose needles in which the side orifices are profiled to direct a fluid flowing along the bore of the needle and out through the orifices forwards, i.e. in the direction in which the needle is pointing. The needles disclosed therein are not disclosed or suggested for use in a vial filling operation.

It is an object of this invention to provide an improved vial filling apparatus based on improved needles, addressing these problems among others. Other objects and advantages of this invention will become apparent from the following description.

According to this invention an apparatus for introducing a liquid into a pharmaceutical container having a puncturable closure is provided, comprising;

a hollow needle suitable for passing through the closure, the needle comprising a tubular conduit defined by a side wall and having an internal bore for the flow of a fluid along the bore in a flow direction, the conduit terminating externally at a pointed end, the bore terminating internally at a closed end, at least one orifice through the side wall for the exit of fluid flowing along the bore, the at least one orifice being oriented to direct liquid flowing along the bore in a direction

having a component parallel to the flow, the conduit having at least one vent groove in its outer surface;

means to cause the needle to puncture the closure to the extent that the at least one orifice is within the container;

means to cause the liquid to flow along the bore;

means to withdraw the needle from the container and closure.

The orientation of the orifice to direct liquid flowing along the bore in a direction having a component parallel to the flow direction may be achieved by an orifice which has a perimeter surface through the side wall converging toward the upstream direction so as to direct a flow of fluid passing through the orifice from the bore toward the outside of the needle in a direction which has a component in the downstream direction.

Herein the term "downstream" refers to the general direction between the end of the needle into which fluid is introduced and the pointed end, and "upstream" refers to the opposite direction.

The benefit of such an alignment of the perimeter surfaces of the bore is that fluid exiting through the orifice is thereby directed in the downstream direction, rather than exiting substantially perpendicularly to the downstream direction.

Preferably the conduit is cylindrical and there are two orifices with their centres 180° apart i.e. on opposite sides of a diameter of the conduit.

Preferably the orifice(s) is(are) elongate in the longitudinal direction of the conduit, for example being oval.

Preferably the total cross sectional area of the one or more orifice is substantially the same +/- 20% as the cross sectional area of the bore of the conduit so that flow of fluid out through the orifice(s) from the bore is not restricted.

Preferably the orifice has an upstream perimeter surface through the side wall inclined to converge toward the upstream direction. Preferably the orifice has a downstream perimeter surface through the side wall inclined to converge toward the upstream direction. If both upstream and downstream perimeter surfaces are inclined to converge with the upstream direction they may incline parallel to each other. Preferably the angle of convergence toward the upstream direction of the

upstream and if present downstream perimeter surface of the orifice is at an angle of 10-60°, more preferably ca. 30°, with the upstream direction.

Preferably the perimeter of the orifice is rounded rather than sharp to reduce the possibility of cutting of the closure by sharp edges of the orifices as they pass through an elastomer vial closure, and the consequent formation of particles of the closure material.

Preferably the internal closed end of the bore comprises surfaces that converge toward the upstream direction.

Preferably these surfaces converge toward the upstream direction in the form of an edge with its ridge pointing in the upstream direction, being more preferably a sharp knife edge between the surfaces of the closed end. Preferably the angle of convergence is the same as that of one or more of the converging perimeter surfaces of the orifice.

Preferably if there are two orifices the edge formed by these converging surfaces of the internal closed end of the bore is aligned with the line of its ridge perpendicular to the axis between the two orifices. The sloping alignment of these surfaces of the edge is preferably the same as that of the upstream perimeter surface of the orifice, i.e. at the angles disclosed above, and preferably merges smoothly with the perimeter of the orifice.

Preferably the converging surfaces of the internal closed end of the bore, e.g. the ridge of a so-formed edge, extend in the upstream direction at least as far as the upstream perimeter of the orifice. The edge is preferably part of a so called "saddle" shaped surface.

The advantage of such converging internal surfaces, particularly this edge, is that flow of fluid exiting from the orifice is guided thereby in the downstream direction, and such an edge, e.g. in the form of a saddle shaped surface provides no flat surface for particles or other contamination to rest upon.

The pointed end may be a pyramid with three faces. The apex of such a pyramid may enclose an angle of 30-60°. Preferably the pointed end is a conical shape, suitably having a cone angle of 15-30° , preferably 20-25°, at the pointed tip. The benefit of a cone shape over a pyramidal shape is that the conical shape damages less of the elastomer material as it punctures the closure, whereas a

pyramid can leave a larger "star" shaped puncture hole with cuts radiating from the apexes of the polygonal e.g. triangular, section of the pyramid. Such a cone shape can generate no particles of the closure material is it punctures the closure.

Therefore a specific preferred form of the needle for the apparatus of this invention comprises:

a cylindrical tubular conduit defined by a side wall and having an internal bore for the flow of a fluid along the bore in an flow direction, the conduit terminating externally at a conically pointed end, the bore terminating internally at a closed end, at least one orifice through the side wall for the exit of fluid flowing along the bore,

wherein at least one orifice has upstream and downstream perimeter surfaces through the side wall converging toward the upstream direction at an angle between 10-60° relative to the upstream direction,

the total cross sectional area of the one or more orifice is +/- 20% of the cross sectional area of the bore of the conduit,

and the internal closed end of the bore comprises surfaces that converge toward the upstream direction.

Preferably the pointed end of the conduit is provided as a separate plug part which can be plugged into the downstream open end of the conduit. Such a plug part may consequently comprise a male plug end which can be inserted into the open downstream end of the bore of a tubular conduit, the plug part having a pointed end longitudinally opposite this male plug end, the plug end being shaped into the above-described edge. Such a plug end may be welded into the bore of the conduit.

The conduit is also provided on its external surface with one or more vent groove to allow the atmosphere within a container such as a vial to escape as fluid is introduced into the container. Suitably such a groove may extend in a direction parallel to the longitudinal axis of the conduit, e.g. parallel to the upstream-downstream direction. The length of such a groove need be sufficient that when the needle has punctured the closure to its fully intended extent one end of the groove is within the container and the other end is exposed outside of the container. There may be one or more such vent groove, preferably two or more vent grooves. It is

found that the venting efficiency can influence the vial filling speed, and four grooves can be better for filling larger volume vials. It is found that when the needle is used to puncture an elastomer closure, e.g. of a vial, the elastomer tends to fill the vent groove(s). It is found that this can be avoided by a groove which is of a profile, cut across the axis of the needle, which has sharp corners, which are not easily completely filled by the elastomer. For example the groove may have a rectangular profile. Plural grooves may be regularly spaced around the circumference of the conduit. An alternative arrangement is four grooves arranged in two pairs, each pair disposed on opposite sides of a diameter of the conduit, grooves in each pair, with a 20-50°, e.g. 40 $\pm 5°$ angular spacing between the grooves of the pair. The groove may for example have a depth of ca. 50% of the thickness of the conduit wall, e.g. 0.2 mm deep, and a width 0.2-0.4 mm. It is preferred that at the ends of the groove(s) the groove accomodates gradually to the outer profile of the conduit, rather than at a sharp step, to avoid cutting particles of the elastomer of the closure on insertion or removal of the needle through the closure. Needles having these dispositions of vent grooves are believed to be novel.

The above-mentioned guiding of the flow of fluid exiting from the bore into the downstream direction has a further advantage in reducing the possibility of the fluid being sprayed in the upstream direction and entering the vent groove.

The conduit and plug part as described above may be made of metals such as stainless steel as commonly used in the art. Typically the conduit may have an outside diameter ca. 2-3 mm, and the bore may have an internal diameter 1-2 mm, with a side wall thickness typically 0.3-0.5 mm.

The container may suitably be a pharmaceutical vial having a puncturable elastomeric closure. Suitable vials are disclosed for example in WO 04/018317. Such a vial for example has an upwardly-facing mouth opening bounded by a rim in the form of a flange having upper and lower surfaces extending transverse to its upper-lower axis, and has an elastomer closure part shaped to sealingly engage with the mouth opening, having a lower surface to face the interior of the vial and an opposite upper surface to face away from the vial, and capable of being punctured by a needle is inserted into the mouth opening of the vial, and has a clamp part engaged with the flange around the rim of the mouth opening of the vial by a

resilient snap-fit engagement of a snap fit part of the clamp part underneath a downwardly facing surface of such a flange part, and bearing upon the upper surface of the closure part to hold the closure part in a closing relationship with the mouth opening.

The means to cause the needle to puncture the closure may comprise means to hold the needle and support the container, e.g. a vial, and cause them to move relatively together along the longitudinal axis of the needle. For example the container may be a vial supported with its closure uppermost, and the needle may be held above the container and moved downwardly toward the closure. Suitably the container such as a vial may be supported on a conveyor below the needle holder. The means to withdraw the needle from the container and closure may comprise the same means but operating in a reverse reciprocal movement. The means to support the container, particularly a vial, should incorporate means to restrain the container against the withdrawing force of the needle. A suitable means is for example disclosed in WO-A-04/026735. For example the vial may have a bottom opposite its mouth opening which fits into a vial stand, and this means may bear upon the stand to hold the combination of vial and stand down against the withdrawing force.

The means to cause the liquid to flow along the bore may comprise a conventional metering pump connected to a supply of the liquid. Such a pump may be operated to deliver a metered amount of the liquid into the container, and may be controlled to that the liquid is only delivered whilst the orifice is within the container. In another aspect the invention provides a process for making a hollow needle as described above comprising the steps of:

(1) providing a tubular conduit defined by a side wall and having an internal bore for the flow of a fluid along the bore in an flow direction, the bore having an open end;

(2) providing a plug part for the open end, the plug part having a longitudinal axis and being adapted to longitudinally mate with the open end of the bore and having an end surface and an opposite end,

(3) mating the plug part longitudinally with the bore,

(4) cutting at least one orifice through the side wall in a direction converging toward the upstream direction and forming the end surface of the plug part into side surfaces that converge toward the upstream direction,

(5) before or after any of steps (1) to (4) forming the opposite end of the plug part into a point.

Preferably prior to step (3) the end surface of the plug part is formed e.g. cut into the shape of a valley with its bottom extending across the end surface perpendicular to the longitudinal direction, preferably a "V" or "U" sectioned valley.

In step (4) the orifice is cut e.g. by drilling from a direction parallel to the line of the bottom of the valley. Cutting in this preferred way can form the above mentioned saddle shaped closed end surface of the bore.

Preferred features of the so-made needle are as disclosed above.

For example in step (3) the plug part may be welded e.g. laser welded to the conduit side wall when in place in the bore. Preferably after being made as described above the outer surface of the needle is polished, e.g. electropolished, to remove burrs but not to produce a surface that is so smooth that there is high friction between the needle and a vial closure which it punctures.

The vent groove(s) may be made in the outer surface of the conduit at any stage in the above needle-making process. The vent groove(s) may be made using a milling tool which penetrates the outer surface of the conduit progressively.

In another aspect the invention provides a process for introducing a fluid into a puncturable container comprising the steps of;

(1) inserting the point of a needle as described above into the interior of the container by puncturing the container,

(2) flowing a fluid along the bore of the needle in the flow direction,

(3) causing the fluid to exit the needle through the one or more orifice and thereby enter the container, then

(4) withdrawing the needle from the container.

For example the container may be a pharmaceutical vial having a puncturable closure and the fluid may be a liquid medicament.

The invention will now be described by way of example only with reference to the accompanying drawings.

Fig. 1 shows a longitudinal and cross section through the pointed end of a needle of this invention.

Fig. 2 shows sequentially a process for making the needle of Fig. 1.

Referring to Fig. 1 the end of a needle 10 (overall) adjacent to the point 11 is shown. Needle 10 comprises a cylindrical tubular conduit 12 made of stainless steel of circular section of outside diameter 2.4mm defined by a side wall 13 and having an internal circular sectioned bore 14 of inside diameter 1.65 mm, the thickness of the side wall 13 being 0.38 mm. The conduit 12 is suitable for the flow of a fluid (not shown) along the bore 14 in an flow direction indicated by the arrow.

Externally the conduit terminates externally at pointed end 11, which is in shape a cone with a cone angle at its apex of ca. 20-45°. Such a conical profile avoids sharp cutting edges which could form particles of elastomer material as the point punctures an elastomer closure.

There are two orifices 15 through the side wall 13 for the exit of fluid flowing along the bore 14. These orifices are located 180° apart, i. e. diametrically opposite each other on opposite sides of the bore 14. Each orifice 15 is of an oval shape elongated parallel to the upstream-downstream direction. Each of the orifices 15 has an upstream perimeter surface 15A and also a downstream perimeter surface 15B through the side wall 13 converging toward the upstream direction at an angle (A) of ca. 30° with the upstream direction, i.e. parallel to the upstream surface 15A.

The edge 15C of the upstream perimeter surface 15A is rounded to reduce any possibility of the edge 15C cutting material of a closure through which the needle is passed. The total cross sectional area of the two orifices 15, i.e. at the extrapolated inner surface of the bore 14 is substantially the same as the cross sectional area of the bore 14.

The bore 14 terminates at a closed end 16 which is profiled. This closed end 16 of the bore comprises surfaces 17 that converge toward the upstream direction, and which meet at a sharp knife edge ridge 18. The orientation of the line of the edge 18 is perpendicular to the axis between the two orifices 15, i.e. aligned with a

diameter at 90° to the diameter on which are located the orifices 15. The sloping surfaces 17 consequently are intersected by the same diameter that passes through the orifices 15. As is seen in Fig.1 the sloping alignment of the side surfaces 17 of the edge 18 is the same as that of the downstream perimeter surfaces 15B of the orifices 15 so that the surfaces 17 merge smoothly with the perimeter surface 15B of the orifice 15. The edge 18 extends in the upstream direction beyond the upstream perimeter 15A of the orifice.

The pointed end 11 is provided as a separate plug part 20 which can be plugged into the downstream open end 21 of the bore. Plug part 20 comprises a male plug end 22 which can be inserted into the open downstream end 21 of the bore 14 of the tubular conduit 12 and has an opposite pointed end part 23 comprising the point 11, the plug end 22 being shaped into the above-described edge 18 with its sloping side surfaces 17.

The conduit 12 is also provided externally with two diametrically opposite vent grooves 24, each ca. 0.2mm deep, visible in Fig. 2. The longitudinal ends 24A of each groove 24 accomodates gradually to the outer profile of the conduit 12, rather than with a sharp step.

It will be apparent that fluid flowing along bore 14 will be directed into a direction having a component in the downstream direction upon exiting through the orifices 15, because of the directing effect of the fluid guide surfaces 15A, 15B, 17.

Fig. 1A shows a cross section through the conduit 12 of the needle 10 of Fig. 1 at the line A- -A of Fig. 1. The two vent grooves 24 more clearly seen in Fig. 2 can be seen situated 180° apart around the outer c ircumference of the conduit 12. Fig. 1B shows an alternative cross section through the conduit 12 of the needle 10 of Fig. 1 at the line A- -A of Fig. 1. The two vent grooves 24 more clearly seen in Fig. 2 can be seen situated 180° apart around the outer circumference of the conduit 12. The thickness of the steel wall of the conduit 12 is ca. 0.38mm. The two vent grooves 24 each have a width of ca. 0.4 mm and a depth of ca. 0.2 mm. Fig. 1C shows another alternative cross section through the conduit 12 of the needle 10 of Fig. 1 at the line A- -A of Fig. 1. Four vent grooves 24 are seen, disposed in two pairs situated 180° apart across a diameter of conduit 12. The grooves 24 of each pair are spaced ca. 40° apart around the outer

circumference of the conduit 12. The thickness of the steel wall of the conduit 12 is ca. 0.40mm, the conduit diameter being 2.4mm. The four vent grooves 24 each have a width of ca. 0.2 mm and a depth of ca. 0.2 mm. In Figs 1B and 1C the edge between the sides of the groove 24 and the outer surface of conduit 12 is radiused at ca. 0.05 mm to avoid cutting particles of a closure as the needle punctures the closure.

Referring to Fig. 2 a process for making the needle of Fig. 1 is shown sequentially.

Referring to Fig. 2A step (2) of the above-described process is shown. A plug part 30 for the open end of the bore 14 of a conduit is shown. The plug part 30 is elongated along the vertical longitudinal axis. One end 31 is formed into a male plug adapted to longitudinally mate with the open end 21 of the bore of a conduit, i.e. being of an outside diameter corresponding to the internal diameter of the open end 21 of the bore 14 so that end 31 is a tight fit in open end 21. The opposite end 32 is formed into a pyramidal point. The end surface 31 of the plug part 30 has been cut into the shape of a "V" sectioned valley 33 with its bottom extending across the end surface 31 in the direction B- -B perpendicular to the longitudinal direction. There is an abutment ledge 34 around the part of the plug part 31 closest to the point 32 to limit the extent to which the part 31 can enter the bore 14.

As seen in Fig. 2B the plug part 30 has been mated with the open end of the tubular conduit 12, i.e. step (3).

Fig. 2C shows step (4). Two orifices 15 have been drilled at diametrically opposite positions through the side wall 13 of conduit 12 in a direction converging toward the upstream direction. The line B- -B of the bottom of the valley 33 is aligned parallel to the diameter of the conduit joining the two orifices 15. The downstream perimeter surface 15B of orifice 15 is visible.

Fig 2D shows the rounding of the upstream perimeter surfaces 15A of the orifices 15 using a tool 35, to form the rounded edge 15C.

Fig 2E shows in an exploded view how the drilling of the orifices 15 through the side wall 13 has formed the end surface 16 of the plug end 22 of plug part 20 into side surfaces 17 that converge toward the upstream direction to form the edge 18, and which form part of an overall "saddle" shaped surface, i.e. with

surfaces 19 inclined relative to the upstream-downstream direction and generally in planes perpendicular to the planes of the side surfaces 17.

Fig. 3 shows how the needle of Fig. 1 is used in an apparatus of the invention. As seen in Fig. 3A a pharmaceutical vial 31 is provided having a puncturable elastomer closure 32, held in place in a closing relationship with the mouth of the vial 31 by a clap part 33 which has a central aperture 34 through which the closure 32 is exposed. The interior of vial 31 and the part of closure 32 exposed within aperture 34 have been pre-sterilised.

A hollow needle 35 of the type shown and described with reference to Figs 1 and 2 is supported above vial 32, with its point downwards and aimed at closure 32 through aperture 34. Needle 35 is supported by holder 36 which can be moved reciprocally upwardly and downwardly relative to vial 31 by suitable means (not shown). Holder 36 also connects needle 35 to a source (not shown) of a liquid via line 37.

Vial 31 has its bottom held by a base 38 which enable vial 31 to be held down onto a conveyor (not shown) by which vial 31 may be moved underneath needle 35 into the relationship shown.

As seen in Fig 3B, the needle 35 has been moved downwardly by means of a corresponding downward movement of holder 36, so that needle 35 punctures and passes through the closure 32 with orifices shown 15 in Figs 1 and 2 within vial 31.

As seen in Fig 3C, a liquid 39 is caused to flow along line 37 through conduit 12 (as seen in Figs 1 and 2) of the needle 35, to exit via the orifices 15 into vial 31. The orientation of the orifices 15 directs the liquid 39 to flow out of the needle 35 in a direction having a component parallel to the flow direction, i.e. having a downward component as seen in Fig. 3C. The flow of liquid 39 is seen to be in a direction at a non-zero, non-perpendicular direction to the longitudinal axis of the needle 35. Flowing in this direction the liquid 39 is directed away from the underside of closure 32 and the upper regions of the interior of vial 31 toward the bottom of vial 31. The vent groove shown 24 in Fig. 2 in the outer surface of needle 35 has a length sufficient that when the needle 35 has punctured the closure 32 to its fully intended extent as seen in Fig 3C one end of the groove 24 is within

the vial 31 and the other end is exposed outside of the vial, so that air within the vial 31 can escape via the groove 24 as shown 310.

As seen in Fig 3D a reciprocal upward movement of the holder 36 and needle 35 has caused the needle 35 to be withdrawn from the vial 31 and closure 32. The vial 31 may be held down by a holding means (not shown) applied to the base 38. The residual puncture hole 311 may be heat sealed.

The entire operation shown in Figs 3A – 3D is preferably performed under a downward laminar flow of sterilised air (not shown).